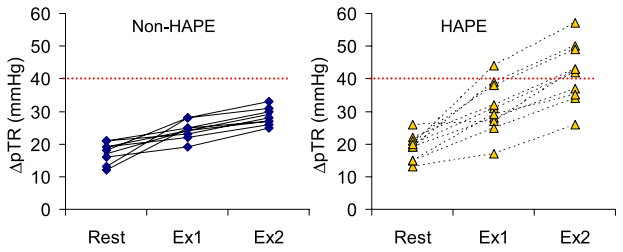

Figure 1 **Individual Response of ΔpTR**

Individual response of pressure gradient across tricuspid valve (ΔpTR) at low altitude from rest to low-intensity exercise (Ex1 = 20% and Ex2 = 40%, respectively, of previously tested maximal exercise capacity) in high altitude pulmonary edema (HAPE)-susceptible subjects **(right)** compared with control subjects (non-HAPE). **Red dotted lines** indicate approximate upper limit of normal during exercise.

Diagnosis of pulmonary hypertension is often delayed because of nonspecific symptoms (5), which may be even more so regarding exercise-induced pulmonary hypertension. Therefore, PAP measurement during exercise may be helpful in subjects with unexplained dyspnea on exertion, some of which are considered to have diastolic heart failure. High altitude pulmonary edema shows that it is not mandatory to have a significantly elevated left-sided filling pressure to develop pulmonary edema, but that alterations within the pulmonary vasculature can be the causative factor (6). Pulmonary vascular hyperreagibility in response to hypoxia (i.e., HAPE susceptibility) may also explain why some patients with pulmonary diseases develop pulmonary hypertension whereas others do not. In patients with chronic hypoxia, HAPE susceptibility might facilitate pulmonary vasoconstriction.

Since this study does not address pathogenetic issues, we are unable to shed further light on the underlying cause of HAPE susceptibility. Importantly, this study provides preliminary results only. The small number of subjects included contains some risk of a false-positive finding. Furthermore, whether some of the HAPE-susceptible subjects presented will actually develop clinical signs of pulmonary hypertension remains speculative. A long-term follow-up study is necessary to address this question.

Nevertheless, the relatively high prevalence of HAPE susceptibility and the fact that more than half of the HAPE-susceptible subjects developed pulmonary hypertension at a workload corresponding to daily activities with structural changes indicating right-sided cardiac pressure overload highlight the need for more frequent consideration of exercise-induced pulmonary hypertension as potential cause of exertional dyspnea.

Stephanie Kiencke, MD
Alain Bernheim, MD
Marco Maggiorini, MD
Manuel Fischler, MD
Schlomo V. Aschkenasy, MD
Lorenz Dorschner, MD
Johann Debrunner, MD
Konrad Bloch, MD
Heimo Mairbäurl,PhD
***Hans Peter Brunner-La Rocca, MD**

*Cardiology
University Hospital Basel
Petersgraben 4
4031 Basel
Switzerland
E-mail: brunnerh@uhbs.ch

doi:10.1016/j.jacc.2007.10.018

Please note: Drs. Kiencke and Bernheim contributed equally to this work. The authors thank Toshiba Switzerland AG for providing and transporting the Toshiba Aplio 80 ultrasound equipment.

REFERENCES

1. Grunig E, Mereles D, Hildebrandt W, et al. Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. J Am Coll Cardiol 2000;35:980–7.
2. Bartsch P, Maggiorini M, Mairbaurl H, Vock P, Swenson E. Pulmonary extravascular fluid accumulation in climbers. Lancet 2002;360:571.
3. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med 2006;145:497–506.
4. Bossone E, Rubenfire M, Bach DS, Ricciardi M, Armstrong WF. Range of tricuspid regurgitation velocity at rest and during exercise in normal adult men: implications for the diagnosis of pulmonary hypertension. J Am Coll Cardiol 1999;33:1662–6.
5. Runo JR, Loyd JE. Primary pulmonary hypertension. Lancet 2003;361:1533–44.
6. Maggiorini M, Melot C, Pierre S, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. Circulation 2001;103:2078–83.

Letters to the Editor

Left Atrial Dimension in Stress Echocardiography

We read with interest the recent study by Bangalore et al. (1) evaluating the prognostic significance of left atrial (LA) enlargement in patients undergoing stress echocardiography. The authors demonstrate that left atrial dimension provides incremental prognostic significance in patients referred for stress echocardiography, irrespective of the presence of inducible ischemia. Although we applaud the authors for highlighting the importance of left atrial enlargement in this patient population, there are several methodologic concerns which profoundly limit the applicability of their findings to clinical practice.

First, the use of M-mode linear dimension to measure left atrial volume is inaccurate and varies widely among individual readers (2). We have previously shown that left atrial volume is most

accurately estimated by 2-dimensional (2D) echocardiography using biplane methods (area–length or method of discs) (3); this approach is recommended by the American Society of Echocardiography for use in clinical trials (4). Left atrial dimension consistently underestimates left atrial volume and is therefore a specific but insensitive test for left atrial enlargement (5). As such, a significant proportion of patients with true left atrial enlargement were likely categorized as normal. The authors' qualification that "unidimensional measurement is still the most common method worldwide to quantify LA size," although true, is not adequate justification for the investigative use of an inferior measurement. A suitable analogy would be the use of urinary dipstick testing rather than serum glucose measurement to determine the prevalence of diabetes in a study population.

Second, the resting ejection fraction used in the study analysis was based on visual estimation or "eyeballing." This technique is not only inaccurate in determining ejection fraction compared with 2D measurement techniques, but also suffers from wide interobserver variability and poor reproducibility (6). Moreover, the mean ejection fraction in the patients with dilated left atria was 48%, suggesting established systolic dysfunction at baseline rather than "relatively preserved [left ventricular] ejection fraction," as the authors contend.

Third, the authors did not report or correct for Doppler indices of diastolic dysfunction in the multivariate analysis. If, as they suggest, left atrial size is a marker of the severity and duration of diastolic function, then the independent prognostic value of left atrial enlargement cannot be established without taking diastolic dysfunction into account.

Given these methodologic concerns, the authors' conclusion that left atrial size should be routinely incorporated in the prognostic interpretation of stress testing is not justified and furthermore would be unlikely to impact clinical decision making. For example, in the presence of a positive stress echocardiogram it is doubtful that coronary angiography would be averted because of the single measurement of a small left atrial dimension. Conversely an enlarged left atrial dimension in the setting of a normal stress echocardiogram is of unclear significance and would not, on its own, merit further invasive workup.

Ramin Farzaneh-Far, MD
***Nelson B. Schiller, MD, FACC**

*Box 0214, Department of Medicine
University of California
San Francisco, California 94143-0214
E-mail: schiller@medicine.ucsf.edu

doi:10.1016/j.jacc.2007.09.047

REFERENCES

1. Bangalore S, Yao S, Chaudhry F. Role of left atrial size in risk stratification and prognosis of patients undergoing stress echocardiography. J Am Coll Cardiol 2007;50:1254–62.
2. Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: physiologic determinant and clinical applications. J Am Coll Cardiol 2006;47:2357–63.
3. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829–32.
4. Gottdiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echo 2004;17:1086–119.
5. Tsang TSM, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018–23.
6. Sievers B, Kirchberg S, Franken U, et al. Visual estimation versus quantitative assessment of left ventricular ejection fraction: a comparison by cardiovascular magnetic resonance imaging. Am Heart J 2005;150:737–42.

Reply

Although we agree in principle with the views of Dr. Farzaneh-Far and colleagues on the relative value of left atrial (LA) dimension versus volume measurements (as we have acknowledge in the study limitations), there is paucity of data of using any kind of LA size measurement during stress echocardiography. The authors claim that "left atrial volume is most accurately estimated by 2D echocardiography using biplane methods (area-length or method of discs)". Studies have shown that true 3-dimensional (3D) echocardiographic methods or simplified 3D reconstruction method correlate better with magnetic resonance imaging-derived LA volumes (1,2) at the expense of increased complexity of measurement and time. Although the limitations of a LA dimension measurement are well known, given its simplicity, speed, and reproducibility, this measure might be better applicable to patients undergoing stress echocardiography.

Although American Society of Echocardiography recommends using LA volume for use in clinical trials, LA dimension is still the most commonly used measure in large multicenter clinical trials.

In the Cardiovascular Health Study of 5,888 men and women, LA dimension was a significant predictor of future heart failure after controlling for baseline risk factors (3). Similarly, in the Framingham Heart Study (4) and the SPAF (Stroke Prevention in Atrial Fibrillation) trial (5), LA dimension was related to strokes and death in the former and to thromboembolic events (e.g., strokes and transient ischemic attacks) in the latter. Even in the more recent trials like the LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial, LA diameter/height predicted risk of cardiovascular events independent of other clinical risk factors in hypertensive patients with left ventricular hypertrophy (6). In our study we have shown that there was strong interobserver (interclass correlation [ICC] = 0.977) and intraobserver (ICC = 0.980) correlations for the measurement of LA dimension (7).

We have discussed the relative value of using LA size as a marker of diastolic function on the basis of prior studies—it reflects the chronicity and magnitude of the increased left ventricular filling pressure (8) and is thus a marker of the severity and duration of diastolic dysfunction (9). It has been suggested (10) that Doppler indexes of diastolic function reflect filling pressures at 1 point in time and hence LA size might be a better marker, because it represents the chronicity of diastolic function. Given this data from previous studies, we did not correct for Doppler indexes of diastolic dysfunction in the multivariate analysis.

With regard to the accuracy of visually estimated left ventricular ejection fraction, prior studies have shown strong correlation of visually estimated left ventricular ejection fraction with radionuclide angiography (11).

Finally, although we do agree that "enlarged left atrial dimension in the setting of a normal stress echocardiogram is of unclear significance, and would not, on its own, merit further invasive workup," it should be emphasized that, in the setting of a normal